WO2004113314

Publication Title:

NOVEL BORONATE ESTERS

Abstract:

Abstract of WO2004113314

The present invention relates to optically active dihydroxy hexanoate derivatives, boronate esters of formula (IIa) which are useful intermediates for the synthesis of HMG-CoA enzyme inhibitors like atorvastatin, cerivastatin, rosuvastatin, pitavastatin, fluvastatin. Ar = unsubstituted or substituted aryl or heteroaryl, R3 = alkyl from 1 to 8 carbons, aryl or aralkyl, R4 = O, OH, CN or a halogen and a = single bond or a double bond. Data supplied from the esp@cenet database - Worldwide

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(71) Applicant *(for all designated States except US)*: **BIOCON LIMITED** [IN/IN]; 20th Km Hosur Road, Electronics City P.O., Bangalore 561 229, Karnataka (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MELARKODE, Ramakrishan** [IN/IN]; Biocon Limited, 20th Km Hosur Road, Electronics City P.O., Bangalore 561 229, Karnataka (IN). **TIWARI, Sanjay** [IN/IN]; Biocon Limited, 20th Km Hosur Road, Electronics City P.O., Bangalore 561 229, Karnataka (IN). **SURYANARAYAN, Shrikumar** [IN/IN]; Biocon Limited, 20th Km Hosur Road, Electronics City P.O., Bangalore 561 229, Karnataka (IN). **KHEDKAR, Anand** [IN/IN]; Biocon Limited, 20th Km Hosur Road, Electronics City P.O., Bangalore 561 229, Karnataka (IN).

(74) Agents: **ANAND, Pravin** et al.; Anand and Anand Advocates, B-41 Nizamuddin East, New Delhi 110 013 (IN).

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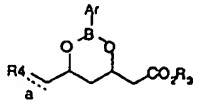
(54) Title: NOVEL BORONATE ESTERS



(IIa)

(57) Abstract: The present invention relates to optically active dihydroxy hexanoate derivatives, boronate esters of formula (IIa) which are useful intermediates for the synthesis of HMG-CoA enzyme inhibitors like atorvastatin, cerivastatin, rosuvastatin, pitavastatin, fluvastatin. Ar = unsubstituted or substituted aryl or heteroaryl, R3 = alkyl from 1 to 8 carbons, aryl or aralkyl, R4 = O, OH, CN or a halogen and a = single bond or a double bond.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE OF THE INVENTION

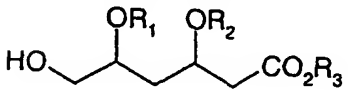
Novel Boronate esters

FIELD OF THE INVENTION

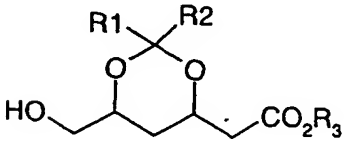
The present invention relates to optically active dihydroxy hexanoate derivatives of formula IIa and more particularly to compounds of formula II which are useful intermediates for the synthesis of HMG-CoA enzyme inhibitors like atorvastatin, cerivastatin, rosuvastatin, pitavastatin, fluvastatin.

BACKGROUND OF THE INVENTION

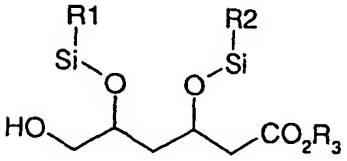
Esters and derivatives of the formula 1,



where R_1 and R_2 are independently chosen alkyl of one to three carbons and R_3 is alkyl of from 1 to 8 carbon atoms, alternatively compounds of formula 1a,



wherein R_1 and R_2 are independently chosen from alkyl of one to three carbons, phenyl or R_1 and R_2 taken together as -(CH2)n- wherein n is 4 or 5 and R_3 is alkyl of from 1 to 8 carbon atoms and also compounds of Formula 1b



wherein R_1 and R_2 are alkyl of from 1-5 carbons and R_3 is as defined above is a valuable structural element for synthesizing

compounds, which are known as anti-hypercholesterolemic agents having an inhibitory effect on HMG-CoA reductase.

EP 0 319 847 describes a process for the preparation of compounds of formula 1 starting from L-Malic acid. This process, however, suffers from the fact that the process is not industrially scalable and also possesses purification problems due to the non-crystalline nature of the intermediates.

US 5,399,722 describe a process starting from commercially available ethyl ω-cloroacetoacetate or its benzyloxy derivative. The disadvantages of this process are that a stereo selective reduction using a costly ruthenium-BINAP catalyst in employed and the desired compound of formula 1 is obtained in six steps.

US 5,481,009 describe a process starting from 4-phenyl-3-butenoic acid in about 5 steps. The process uses expensive materials like - N, O-Dimethyl hydroxylamine and hazardous steps (ozonolysis) to obtain the desired product.

US 5,998,633 describes a process for the preparation of protected esters of 3,4-dihydroxy butyric acid from a carbohydrate moiety which is transformed into the desired 3,4-dihydroxy butanoic acid derivatives in about 4 steps. The 3,4-dihydroxy butanoic acid derivative is then functionalized into compounds of formula I involving a multiple number of steps.

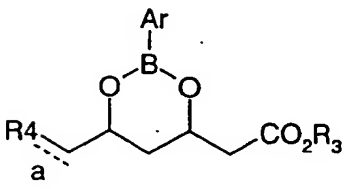
US 6,140,527 describes a process for producing butyric acid derivatives starting from a butene derivative followed by reaction with an addition reagent capable of adding across the double bond. However, this procedure does not afford chiral molecules and hence necessitates the need for a resolution step.

EP 0 104 750 describes a process for the preparation of 5-hydroxy-3-oxo pentanoic acid derivatives by alkylation of 3-hydroxybutyrate derivatives. The derivatives mentioned in this patent are racemic molecules and thus necessitating a resolution step.

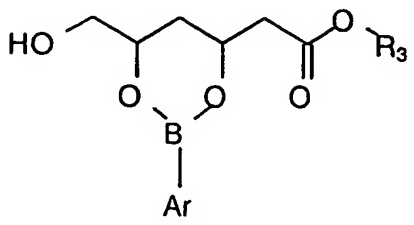
The objective of the present is to provide a simple and industrially scalable process for the preparation of derivatives of formula I starting from commercially available and inexpensive malic acid.

Summary of the invention

To achieve the said object the present invention provides a product of formula IIa and more particularly a compound of formula II



Formula IIa



Formula II

wherein

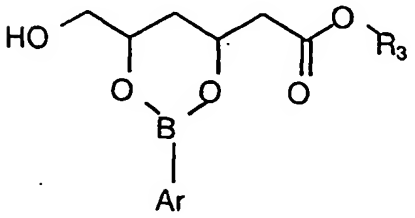
Ar = unsubstituted or substituted aryl or heteroaryl

R_3 = alkyl from 1 to 8 carbons, aryl or aralkyl

R_4 = O, OH, CN or a halogen and

a = single bond or double bond

The present invention also provides for a process for the manufacture of compounds of formula II

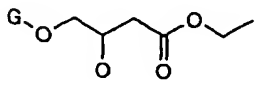


Ar = unsubstituted or substituted aryl or heteroaryl

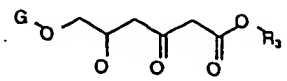
R_3 = alkyl from 1 to 8 carbons, aryl or aralkyl

which comprises of:

(a) reacting compound of formula III with the anion of tertiary butyl acetate to give a compound of formula IV, where G is tetrahydropyranyl, tert-butyldimethyl silyl or trityl and R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl,

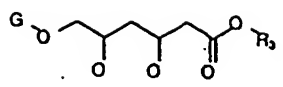


Formula III



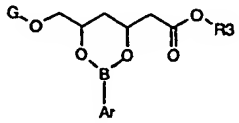
Formula IV

(b) subjecting compound of formula IV to reduction to give a compound of formula V, where G is tetrahydropyranyl, tert-butyldimethyl silyl or trityl and R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl,



Formula V

(c) protecting the compound of formula V with $ArB(OH)_2$ to give a compound of formula VI, where Ar is unsubstituted or substituted aryl or heteroaryl, G is tetrahydropyranyl, tert-butyldimethyl silyl or trityl and R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl, and

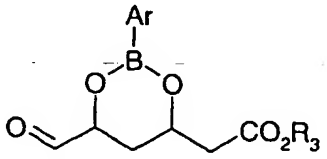


Formula VI

(f) deprotection of the compound of formula VI using mild acid catalyst to give a compound of formula II.

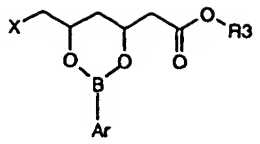
Said $ArB(OH)_2$ is boronic acid.

The compound of formula II is oxidized to a compound of formula VIII, where R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl and Ar is unsubstituted or substituted aryl or heteroaryl using pyridinium chloro chromate or DMSO/oxalyl chloride.



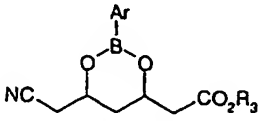
Formula VIII

The compound of formula II is further converted to a compound of formula IX, where R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl, Ar is unsubstituted or substituted aryl or heteroaryl and X is a halogen.



Formula IX

The compound of formula IX is further converted to a compound of formula VII, where R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl, Ar is unsubstituted or substituted aryl or heteroaryl.



Formula VII

The product of formula IIa and more particularly of formula II are used in the synthesis of atorvastatin, cerivastatin, pitavastatin, fluvastatin or rosuvastatin.

Detailed Description of the invention

Compound of formula II serves as a good intermediate for the synthesis of important substrates, which are useful in the synthesis of statins. Compound of formula II can be converted into a facile leaving group by treating with tosyl chloride, methane sulfonyl chloride and the resulting intermediate can be displaced with cyanide to give compounds of formula VII.

Compound of formula II can be converted to formula IX by reacting with aqueous HBr solution or by reaction with triphenyl phosphine and CBr_4 which is then converted to compound of formula VII.

Compound of formula II can be oxidized using standard procedures to give a compound of formula VIII.

The present invention relates to optically active dihydroxy hexanoate derivatives of formula IIa which are useful intermediates for the synthesis of HMG-CoA enzyme inhibitors like atorvastatin, cerivastatin, rosuvastatin, pitavastatin, fluvastatin.

The invention is further illustrated with examples below, which are not intended to be limiting.

Example 1: Synthesis of methyl 4-triphenylmethyloxy-3-hydroxybutyrate (Formula III)

To 25g of methyl 3,4-dihydroxybutanoate was added to 250ml of DCM and stirred to dissolve and 19.8g of pyridine was charged and cooled to 0°C. 41.4g of trityl chloride was dissolved in 50ml of DMC and was added at 0-5°C for 15 min. The temperature was allowed to rise to RT and was stirred at RT for 17h. Water was added and the layers were separated. The organic layer was washed with brine, dried and concentrated. The residue was triturated with 25ml of cyclohexane and the product was purified to give 15g of the pure product.

NMR ($CDCl_3$) : 4.25 (m, 1H), 3.6 (s, 3H), 3.15 (d, 2H), 2.5 (m, 2H), 7.2-7.4 (m, 15H)

Example 2: Synthesis of tert-butyl 6-triphenylmethyloxy-5-hydroxy-3-oxohexanoate (Formula IV)

To 125ml of THF, 24g of diisopropylamine were charged and was cooled to -15°C. 168ml of 1.2N n-BuLi was added at -15 to -5°C and was stirred for 30min. 21.56g of tert-butyl acetate in 45ml of THF which was pre-cooled to -45°C was added maintaining the temperature between -45 to -25°C for 60min. Cool the reaction mixture to -45°C and 30g of example-1 in THF was added over a

period of 20min and the stirring was continued at -25°C for 90min. Water was added and the layers were separated. The aqueous layer was extracted using EtOAc and the combined organic layers were washed with brine, water, dried and concentrated to give the title compound which was used as such for the next step.

Example 3: Synthesis of tert-butyl 6-triphenylmethyloxy-3,5-dihydroxhexanaote (Formula V)

To the crude material obtained in example-2, 150ml of THF was added followed by 15ml of MeOH and was chilled to -60°C. 26ml of MDEB (50% solution in THF) was added over a period of 20min and stirring was continued for a further 30min. The reaction mixture was cooled to -80°C and 5g of sodium borohydride was added in portions and the after completion of addition the reaction mixture was stirred for 5h at -78°C. Acetic acid was added to adjust the pH to 7 and water was added. The aqueous layer was extracted using EtOAc, washed with brine, dried and concentrated to give the title compound which was used as such for the next step.

Example 4: Synthesis of tert-Butyl 6-triphenylmethyloxy-3,5-phenylboranatohexanoate (Formula VI)

The crude product from example-3 was dissolved in 100ml of toluene and 5.6g of phenyl boronic acid was added. Water was removed by azeotropic distillation over a period of 3h. The reaction mixture was cooled to RT and toluene was removed under reduced pressure. 30ml of methanol was added and the precipitated solid was filtered to give 10g of the title product.

Example 5: Synthesis of tert-butyl 6-hydroxy-3,5-(phenylboranato)hexanoate (Formula II)

To 5g of the product from example-4 20ml of DCM was added and was chilled to 0°C. 5ml of TFA was added and was stirred at 20°C for 6h. Water was separated and the organic layer was washed with bicarbonate, brine, dried and concentrated to give the title product, which was purified by column chromatography.

NMR ($CDCl_3$) : 7.7-7.8 (m, 2H), 7.4-7.5 (m, 1H), 7.3-7.4 (m, 2H), 4.5 (m, 1H), 4.2 (m, 1H), 3.6 (m, 1H), 3.5 (m, 1H), 2.55 (m, 1H), 2.45 (m, 1H), 2.0 (m, 1H), 1.7 (m, 1H) 1.5 (s, 9H)

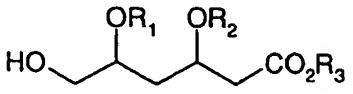
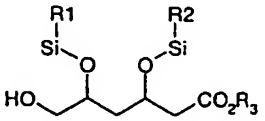
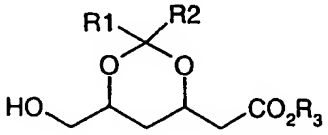
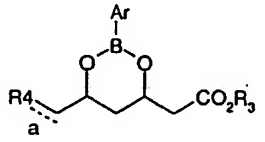
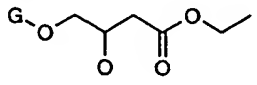
Example 6: Synthesis of tert-butyl 6-cyano-3,5-(phenylboranato)hexanoate (Formula VII)

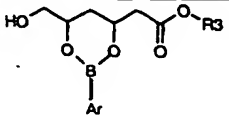
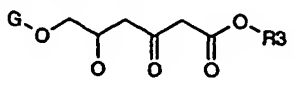
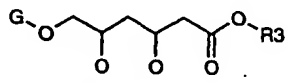
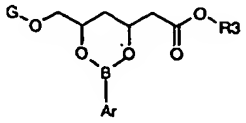
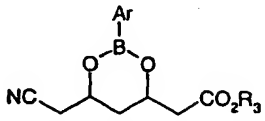
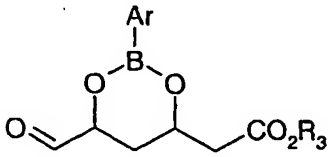
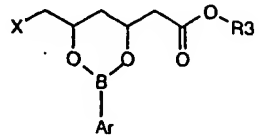
5g of the product obtained from example 5 was taken in dichloromethane (50mL) and pyridine (10mL) was added. The contents were cooled to -10°C and methanesulfonyl chloride (1 eq) was added drop wise. After 5-6 hours of stirring at 0°C, the contents were washed with bicarbonate, water and brine. The solvent was removed under reduced pressure to afford the O-methanesulfonyl derivative, which was used as such for the next step.

The crude mesylate was taken in DMSO (5 vols.) and 1.5 equivalents of potassium cyanide was added. The contents were maintained at reflux for a period of 18-22h. DMSO was removed under reduced pressure and the contents were extracted using ethyl acetate and was washed with bisulfite, brine and solvent was removed under reduced pressure to afford the desired product.

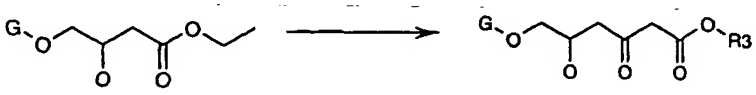
Example 7: Synthesis of t-butyl 6-oxo-3,5-phenylboranatohexanoate (Formula VIII)

4.3g of dimethylsulfoxide was added drop wise to a solution of 2.4ml of oxalyl chloride in 100ml of dichloromethane maintained at -78°C. The mixture was stirred at that temperature for a period of 15min and 5g of the compound from example 5 dissolved in dichloromethane was added drop wise. After stirring for 15min, 17ml of triethyl amine was added and the reaction mixture was allowed to warm to ambient temperature in 2h period. Reaction mixture was concentrated and the residue was dissolved in water and extracted using diethyl ether. Removal of solvent affords the title compound.

Formula I  R1 and R2 are alkyl 1 to 3 carbons R3 is alkyl from 1 to 8 carbons	Formula 1b  R1 and R2 are alkyl from 1 to 5 carbons R 3 is alkyl from 1 to 8 carbons
Formula 1a  R1 and R2 are alkyl 1 to 3 carbons or taken together as -(CH2)n- where n is 4 or 5 R3 is alkyl from 1 to 8 carbons	Formula IIa  Ar = unsubstituted or substituted aryl or heteroaryl R3 = alkyl from 1 to 8 carbons, aryl or aralkyl R4 = OH, CN or X and a =single bond R4 = O and a = double bond
Formula II	Formula III 

 Ar = Unsubstituted or substituted aryl or heteroaryl and R3 is carbon from 1-8 atoms, aryl or aralkyl	G = tetrahydropyranyl, tert-butyldimethyl silyl, trityl
Formula IV  G = tetrahydropyranyl, tert-butyldimethyl silyl, trityl and R3 = alkyl from 1 to 8 carbons, aryl or aralkyl	Formula V  G = tetrahydropyranyl, tert-butyldimethyl silyl, trityl and R3 = alkyl from 1 to 8 carbons, aryl or aralkyl
Formula VI  G = tetrahydropyranyl, tert-butyldimethyl silyl, trityl and Ar = Unsubstituted or substituted aryl or heteroaryl and R3 is carbon from 1-8 atoms, aryl or aralkyl	Formula VII  Ar = Unsubstituted or substituted aryl or heteroaryl and R3 is carbon from 1-8 atoms, aryl or aralkyl
Formula VIII  Ar = Unsubstituted or substituted aryl or heteroaryl and R3 is carbon from 1-8 atoms, aryl or aralkyl	Formula IX  Ar = Unsubstituted or substituted aryl or heteroaryl and R3 is carbon from 1-8 atoms, aryl or aralkyl and x = halogen

Scheme - 1

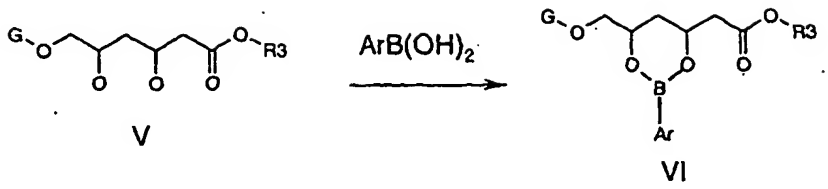


III IV

Scheme - 2

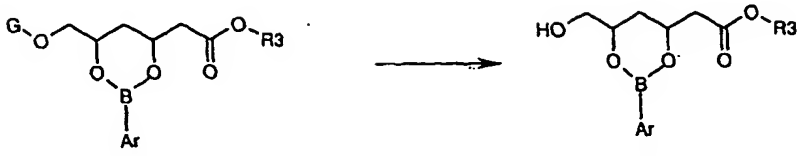
IV V

Scheme - 3



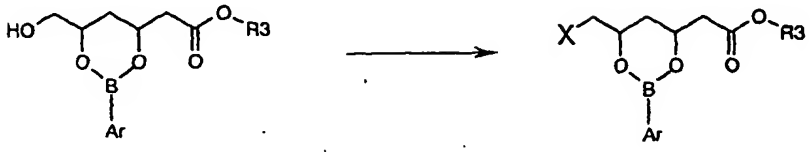
V VI

Scheme - 4



VI II

Scheme - 5

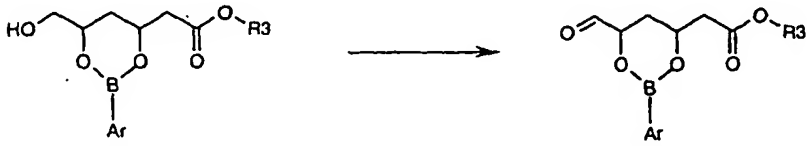


II IX

Scheme - 6

IX VII

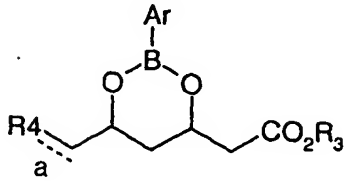
Scheme - 7



II VIII

We claim:

1. The product of formula IIa



wherein

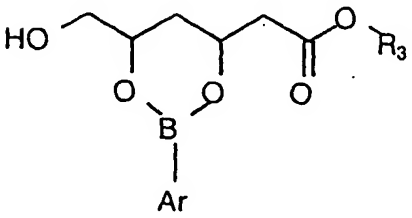
Ar = unsubstituted or substituted aryl or heteroaryl

R_3 = alkyl from 1 to 8 carbons, aryl or aralkyl

R_4 = O, OH, CN or a halogen and

a = single bond or double bond

2. The product as claimed in claim 1 wherein said product is a compound of formula II

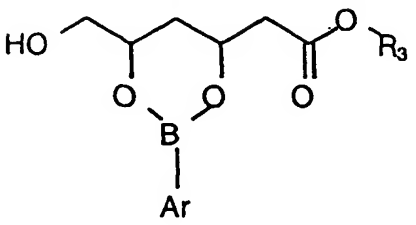


wherein

Ar = unsubstituted or substituted aryl or heteroaryl

R_3 = alkyl from 1 to 8 carbons, aryl or aralkyl

3. A process for the manufacture of compounds of formula II

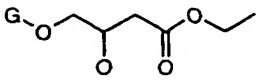


Ar = unsubstituted or substituted aryl or heteroaryl

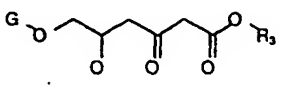
R_3 = alkyl from 1 to 8 carbons, aryl or aralkyl

which comprises of:

(a) reacting compound of formula III with the anion of tertiary butyl acetate to give a compound of formula IV, where G is tetrahydropyranyl, tert-butyldimethyl silyl or trityl and R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl,

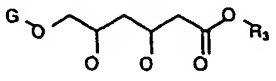


Formula III



Formula IV

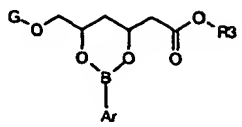
(b) subjecting compound of formula IV to reduction to give a compound of formula V, where G is tetrahydropyranyl, tert-butyldimethyl silyl or trityl and R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl,



Formula V

(c) protecting the compound of formula V with $ArB(OH)_2$ to give a compound of formula VI, where Ar is unsubstituted or substituted aryl or heteroaryl, G is tetrahydropyranyl, tert-

butyldimethyl silyl or trityl and R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl, and

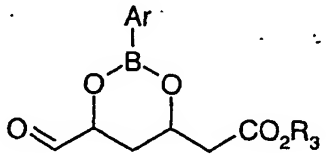


Formula VI

(f) deprotection of the compound of formula VI using mild acid catalyst to give a compound of formula II.

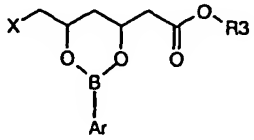
4. A process as claimed in claim 3 wherein $ArB(OH)_2$ is boronic acid.

5. A process as claimed in claim 3 wherein compound of formula II is oxidized to a compound of formula VIII, where R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl and Ar is unsubstituted or substituted aryl or heteroaryl using pyridinium chloro chromate or DMSO/oxalyl chloride.



Formula VIII

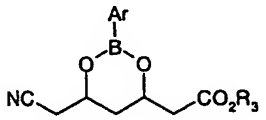
6. A process as claimed in claim 3 wherein compound of formula II is further converted to a compound of formula IX, where R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl, Ar is unsubstituted or substituted aryl or heteroaryl and X is a halogen.



Formula IX

7. A process as claimed in claim 6 wherein compound of formula II is converted to compound of formula IX by reacting compound of formula II with aqueous HBr solution or by reaction with triphenyl phosphine and CBr_4.

8. A process as claimed in claim 6 or 7 wherein compound of formula IX is further converted to a compound of formula VII, where R_3 is alkyl from 1 to 8 carbons, aryl or aralkyl, Ar is unsubstituted or substituted aryl or heteroaryl.



Formula VII

9. The product as claimed in claim 1, used in the synthesis of atorvastatin, cerivastatin, pitavastatin, fluvastatin or rosuvastatin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2004/000175

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 305/12; C12P 17/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATABASES BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN Files Registry, CA: molecular formulae; STN Files Medline, CA, WPIDS: keywords: Streptomyces, oleic, linolenic, statin and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,598,089 (P. HADVARY ET AL) 1 July 1986, cited in the application See whole document	4-13
A	US 4,983,746 (P. BARBIER ET AL) 8 January 1991 See whole document	4
A	EISENREICH ET AL, "Tracer studies with crude U-^{13}C-lipid mixtures: biosynthesis of the lipase inhibitor lipstatin", J Biol Chem, January 1997, Vol. 272, No. 2, p867-874 See whole document	4-13

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2004	19 AUG 2004
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer L.F. MCCAFFERY Telephone No : (02) 6283 2573

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN2004/000175

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	4598089	AU	29478/84	CA	1247547	DK	308584
		EP	0129748	ES	8600650	FI	842422
		GR	82120	HU	34545	IL	72122
		JP	60013777	LU	90302	LV	5747
		MC	1602	MX	9203633	NO	842512
		NZ	208521	PH	19704	PT	78777
		ZA	8404558				
US	4983746	AU	51258/85	CN	85109209	DK	98792
		DK	592585	EP	0189577	IL	77340
		IL	92440	JP	61152664	NZ	214567
		PH	22445	ZA	8509574		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX